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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/482,585	01/13/2000	David G. Hangauer JR.	19226/931 (R-5495)	7206

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EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 06/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/482,585	HANGAUER ET AL.	
	Examiner	Art Unit	
	Padmashri Ponnaluri	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-8, 13-20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-8, 13-20, 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/12/04 has been entered.

2. The amendment and response filed on 4/12/04 has been fully considered and entered into the application.

3. Claims 1, 3-8, 13-20 and 22 are currently being examined in this application.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

5. The disclosure is objected to because of the following informalities: the specification refers to claim 1 method in page 37, lines 13-14.

Appropriate correction is required.

Withdrawn claim rejections

The new matter rejection set forth in the previous office action mailed on 10/16/03 has been withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3-8, 13-20, 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

The instant claims briefly recite a method for identifying inhibitors of protein kinases comprising: covalently attaching at least one first module to a peptide scaffold which comprises a peptide substrate for protein kinase and identifying one or more functional groups on the first module each of which is capable of covalently or non-covalently binding to catalytic residues of the protein kinase; producing one or more combinations of the at least one first module covalently attached to at least one second module comprises an indole, and wherein the at least one second module for the peptide scaffold; screening the one or more combinations of the first

and second module is substituted for peptide scaffold and is capable of occupying the same binding region of protein kinase as the peptide scaffold; screening the one or more combinations of the first an second modules for protein kinases; and selecting combinations of the first and second modules which inhibit protein kinase activity.

The specification disclosure is drawn to a method of identifying inhibitors of protein kinase comprising; a first module having one or more functional groups for binding to catalytic residues of protein kinase are combined with second module which provides for a non-peptide scaffold.

The specification discloses non-peptide protein tyrosine kinase inhibitors having specific formula (i.e., see page 5 of the specification). The specification disclosure is based on the methods taught by a reference publication, which was published after the filing date of the instant application, (i.e., see pages 24 and 50, which refers to a Journal article by Marsilje, 2000, which is required to practice the claimed invention).

The specification discloses a descriptive method (in-silico method or hypothetical method) based on computer modeling of the kinases in identifying protein kinase inhibitors . The specification has not disclosed methods for identifying the functional groups on the first module (scaffold), which would bind to catalytic residues of the protein kinase and use the selected first module having a protein scaffold in attaching to a second module. The specification disclosure does not teach the claimed method steps in identifying a protein kinase inhibitor.

The specification does not disclose identifying (covalently attaching functional groups to the first module) functional groups, which bind to catalytic residues of a protein kinase, and attach a second module to the identified first module by substituting the second module for the

peptide scaffold to form a combination of first and second module. The first module of the instant claims is only defined by the functional characteristics of the compounds, i.e., 'one or more of the functional groups on the first module are capable of covalently or non-covalently binding to catalytic residues of the protein kinase', which is not considered as 'distinguishing characteristics sufficient to show that applicants are in possession of the invention. The specification disclosure is based on the speculation of the 'protein kinase inhibitor activity of the combination of first module and second module.' The specification has not disclosed which of the first module in combination with indole would have the 'protein kinase inhibitor' property.

The specification discloses that the compounds are produced according to claim 1, and does not recite how the compounds are produced. The specification examples are drawn to specific naphthalene scaffold compounds, and indole scaffold compounds as tyrosine kinase inhibitors. The specification disclosure is drawn to specific non-peptide scaffold compounds as protein kinase inhibitors which are distinct from the claimed compounds in which the non-peptide scaffold of the second module is substituted for a peptide scaffold, resulting in a non-peptide scaffold compounds as protein kinase inhibitors.

The specification description does not sufficiently teach the first module having functional groups. The specification discloses various functional groups such as boronic acid as first module, in combination with the non-peptide scaffold (second module), not any fist module having functional groups in combination with second module. The specification discloses compounds with non-peptide scaffold as protein kinase inhibitors, and not the claimed method steps. The specification uses the depicted figure 1, as basis for the claimed method. However, in figure 1, step 1, after the first module capable of binding to the conserved catalytic sites, the

peptide scaffold has been replaced with non-peptide scaffold. However, the non-peptide scaffold (i.e., indole) does not have any specificity elements such that the specificity elements can interact with the substrate specificity sites, so that the compounds (indole scaffold substituted with M1) inhibit the protein kinase activity.

The specification description clearly does not provide adequate representation regarding the open-ended method of instant claim.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that "written description of an invention involving a chemical genus, like a description a chemical species, 'requires precise definition, such as structure or formula or chemical name' of an the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1601 (Fed. Cir. 1993)* [the claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA]. This holding is applicable to the present claimed method because the invention lacks showing of sufficient identifying characteristics or lacks examples of claimed method or identifying a first module whose functional groups bind to the catalytic residues of a protein kinase and attach the selected or identified first module with the functional groups to a second module of the claimed method, to demonstrate possession of claimed generic. The specification does not recite that identifying the first module comprises attaching the first module to a peptide scaffold.

The claimed method recites '.....identifying one or more functional groups on the first module, each of which is capable of covalently or non-covalently binding to catalytic residues of the protein kinase ...', however, the specification disclosure does not give sufficient guidance

on how to identify the first module which have functional groups which can bind to a catalytic sites of a protein kinase. Further the instant claim recites that the '...identifying comprises covalently attaching the first module to a peptide scaffold....'. The specification does not sufficiently teach the structure of the first module such that the starting reagents in the claimed method are known. The specification does not give any guidance on selecting the first module or how to identify the first module having functional groups capable of binding to a protein kinase conserved catalytic sites or which compounds are used as first module.

The specification disclosure is hypothetical and based on identifying individuals scaffolds which could inhibit protein kinases and is not drawn to identifying potential first modules and attaching the identified first module to a second module such that the second module substitutes for the peptide scaffold and then screen for the combination of first and second modules as protein kinase inhibitors. The specification disclosure is based on computer modeling in identifying various functional groups (i.e. first module) in combination with indole scaffold (non-peptide scaffold or second module). The specification description is based on computer modeling studies of protein kinases and use of analogs or different functional group attachment to a first scaffold and screening for protein kinase inhibitors. However, the specification has not disclosed the claimed method of identifying the protein kinase inhibitors. The specification does not have examples or chemical structure of the protein kinase inhibitors identified using the claimed method. Thus the specification lacks written description of the claimed invention.

8. Claims 1, 3-8, 13-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for indole or naphthalene as the non-peptide scaffold, and

the use of specific functional groups as the first module (M1 in table 1), does not reasonably provide enablement for the broad scope of the instantly claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims briefly recite a method for identifying inhibitors of protein kinases comprising: covalently attaching at least one first module to a peptide scaffold which comprises a peptide substrate for protein kinase and identifying one or more functional groups on the first module each of which is capable of covalently or non-covalently binding to catalytic residues of the protein kinase; producing one or more combinations of the at least one first module covalently attached to at least one second module comprises an indole, and wherein the at least one second module for the peptide scaffold; screening the one or more combinations of the first and second module is substituted for peptide scaffold and is capable of occupying the same binding region of protein kinase as the peptide scaffold; screening the one or more combinations of the first an second modules for protein kinases; and selecting combinations of the first and second modules which inhibit protein kinase activity.

The specification discloses hypothetical methods in detecting the different functional groups (M1), which interact with the conserved catalytic sites of particular protein kinases. The specification disclosure is based on known crystal structure of a protein kinases (src) and the functional groups, which can interact with the catalytic sites.

The factors to be considered in determination of undue experimentation are disclosed In re Wands (USPQ 2d 1400: CAFC 1988); the quantity of experimentation necessary: the amount

of direction or guidance presented; the presence or absence of working examples; the nature of the inventions; the state of the prior art; the predictability of the art and the breadth of the claims.

A number of factors would prevent one of ordinary skill in the art from practicing (making and using) the invention without undue experimentation, which are summarized as follows:

a) The specification fail to give adequate direction and/or guidance as to the means of identifying at least one functional group on the first module by attaching the first module to a peptide scaffold and identifying the functional groups on the first module which bind to catalytic residues of the protein kinase; and covalently attaching the selected or identified first module to a second module and substituting the peptide scaffold of the second module for a non-peptide scaffold. The specification fail to give guidance on how to identify a first module or the structure of the first module and use the identified first module covalently attached to a peptide scaffold, to attach to a second module by substituting the second module for a non-peptide scaffold. The specification does not give sufficient guidance on the chemical structure of the first module or the peptide scaffold (except the disclosed pentapeptide (peptide scaffold) based PKA inhibitors) or the first module attached to the peptide scaffold or the second module.

b) The specification working examples are drawn to specific compounds with either naphthalene or indole scaffold compounds as protein kinase inhibitors. The specification does not recite any compounds in which the peptide scaffolds of the second module a substituted for a non-peptide scaffold and use of these compounds as protein kinase inhibitors. The specification enables those skilled in the art to make and use full scope of the claimed invention without undue experimentation. The resulting compounds of the claimed method may not result in any useful

compounds. The specification does not provide an enabling disclosure of the full scope of the claimed invention.

c) The breadth of the claims is open ended regarding the resulting protein kinase inhibitor structure. The compounds in the specification are all drawn to specific non-peptide scaffold compounds (indole or naphthalene), which are substituted with M1 functional groups. The specification disclosure only speculates the utility of the resulting compounds as protein kinase inhibitors.

d) The state of prior art at the time the invention was made is such that the protein kinase inhibitors are specific to the kinases and in general are known to be difficult resulting in non-functional compounds. Protein Kinases are a large class of enzymes. Estimated to be ~ 2,000 distinct protein kinases. Even though the regions of active site of protein kinases are conserved, each particular protein kinases display differing preferences or variation in the active site conformations and adjoining residues

e) The art is unpredictable because organic synthesis (or modifications) and screening for active compounds is unpredictable when applied to compounds of diversity. Moreover, it is not possible to predict, a priori, the compounds that have not prepared previously, especially when the compounds are from a diverse classes of compounds, which lack any core structure that is necessary to elicit a common activity.

Accordingly, unpredictability with respect to the final compound structure, the lack of guidance presented in the specification, the lack of representative examples for making such protein kinase inhibitors necessitate the illustration or further examples demonstrating the

making and use of representative sample of the compounds in order to provide the enablement for the present broadly claimed method.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1, 3-8, 13-20, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite by reciting 'covalently attaching at least one first module to a peptide scaffold.... Identifying one or more functional groups on the first module each of which is capable of covalently or non-covalently binding to catalytic residues of the protein kinase..'. It is not clear what does applicants mean by 'covalently attaching the first module to the peptide scaffold, and identifying the functional groups on the first module which are capable of covalently or non-covalently binding to the catalytic residues of the protein kinase. Does applicants mean that the first module is functional groups. It is not clear, since the throughout the specification discloses that functional groups which are utilized as M1 (i.e., first module). Does applicants mean that the M1 or the first module is a bi-functional compound which covalently binds to the peptide scaffold and capable of binding to the catalytic residues covalently or non-covalently. Applicants are requested to clarify which groups are considered as M1 or first module and the functional groups.

Claim 1 recites the limitation "the same region of the protein kinase" in 15. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the claim does not recite how the first module and second module are attached, and/or the chemical structure of the first module and/or the functional groups of the first module and protein kinase and the peptide scaffold. The claim does not recite how all these reagents are linked together such that the resulting compounds inhibit protein kinases.

Response to Arguments

11. Applicant's arguments filed on 4/12/04, regarding the lack of written description rejection and the scope enablement rejection have been fully considered but they are not persuasive. Note applicants arguments for the above two rejections overlap, and thus addressed in this response together.

Applicants argue that the specification in figures 1-3, and description pages 11-22 discloses the examples of the identification of the functional groups, which bind to the conserved catalytic residues of the protein kinase. And further applicants argue that the specification discloses methods for identification of the functional groups which bind to the conserved catalytic residues of a protein kinase is set forth.

Applicant's arguments have been fully considered and are not persuasive, since applicants are not in possession of all the different functional groups, which can be used in making or designing the protein kinase inhibitors at the time of filing of the instant application. According to the specification disclosure, various different functional groups can be tested to determine which may be useful in preparing the compounds. Thus, the useful groups or

functional groups would only determined after further testing. Thus, applicants are not in possession of the broadly claimed method in which the first module is only defined as having a functional property. Neither the specification nor the claims recite how the first module and the second module are linked such that the resulting compounds have protein kinase activity. As in the applicant's response, the speculative protein kinase inhibitory compounds are determined based on the modeling studies of specific src protein kinase, and the use of pentapeptide scaffold.

And further applicants assert that the specific structures of the functional groups are set forth, as well disclosed correlation between their function and structure based on molecular modeling studies and production and testing of pentapeptide scaffold. Thus, according to applicants assertions that only the disclosed first module as in Table 1 in relation to the pentapeptide scaffold are useful as pp60 c-src inhibitors in combination with indole or naphthalene scaffold.

Applicants argue that the peptide scaffolds of specific protein kinases are known in the art. Whether the peptide scaffolds are well known in the art or not is irrelevant to the presently claimed method. The different peptide scaffolds of different protein kinases may have different peptide sequences, and the non-peptide scaffolds of the instant claim indole in combination with the first module of the instant claims may not inhibit every known protein kinases. Even though the regions of active site of protein kinases are conserved, each particular protein kinases display differing preferences or variation in the active site conformations and adjoining residues.

Applicants assert that detailed examples of producing the protein kinase inhibitors in which second module is naphthalene or indole substituted for a peptide scaffold (set forth in page 40) in combination with first module (i.e., OH). Applicants assertions have been

considered, however are not persuasive because the instant claimed method is not limited to the "OH" as first module in combination of indole as second module. The instant claimed method is drawn to broad genus of compounds as protein kinase inhibitors, not limited to the compounds having selected first module (e.g., OH, boronic acid, or phosphonic acid) covalently attached to the indole scaffold as in applicants arguments. Thus, the rejections of record have been maintained for the reasons of record.

12. Applicant's arguments with respect to the rejection of claims under 35 U.S.C. second paragraph have been considered but are moot in view of the amendments to the claims and the new rejections.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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